IN THE U.S. PATENT AND TRADEMARK OFFICE

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Title:	DETERMINATION OF BIOLOGICAL CONDITIONS USING IMPEDANCE MEASUREMENTS		
Inventor(s):	Stig OLLMAR		
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Commissioner for Patents
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REQUEST FOR RECONSIDERATION

Sir:

In response to the Office Action dated December 10, 2008, Applicants respectfully request that the Examiner reconsider the rejections raised in the outstanding Office Action and find all claims allowable based on the discussion which follows.

All pending claims, claims 14 -17 and 19 - 43 were rejected under 35 U.S.C. §103(a) as being unpatentable over Davies (U.S. Patent No.: 6,922,586 (hereinafter "Davies") in view of Stemme et al U.S. Patent Publication No.: 2004/0054393 (hereinafter "Stemme"). In the rejection, it was alleged that it would have been obvious

to combine the method for diagnosing a condition of skin disclosed in Davies with the electrode probe disclosed in Stemme.

Contrary to the rejection, due to differences in the respective methods, techniques and devices disclosed in Davies and Stemme, one of ordinary skill in the art would not have combined these two dissimilar medical techniques and devices to in any way arrive at the claimed method or apparatus. As it will be discussed in great detail below, each reference is directed to a very different device and diagnostic technique for measuring different physiological parameters for completely different medical purposes.

Applicants respectfully note that references cannot be combined unless there is an apparent reason which would have led one of ordinary skill in the art to combine the references. KSR International v. Teleflex, Inc., 550 U.S. _____ (2007) (hereinafter "KSR). Further, one of ordinary skill in the art must have seen a benefit from altering the closest prior art by adding to it, or removing from it, elements which define differences between the prior art and the claims at issue. KSR. In particular to the rejections in this application, one skilled in the art must have seen a benefit from modifying the closest prior art (identified as the primary references of Davies) to arrive at the claimed invention.

In what will be discussed in great detail below, one of ordinary skill in the art would not have seen any benefit from altering the device of Davies to incorporate the electrode of Stemme to in any way arrive at the claimed invention. Specifically one of ordinary skill in the art would not have seen or recognized any benefit from making such a modification due to differences in which each respective method and devices functions

and is used to measure completely difference physiological parameters for completely different purposes. Furthermore, one of ordinary skill in the art would not have known how to modify the device and method of Davies to incorporate the electrode of Stemme to arrive at an operable device or method.

As an initial point, it must be stressed that the present invention is directed to a method and an apparatus for diagnosing a diseased condition of the skin of a subject, such as the presence of skin cancer, e.g. basal cell carcinoma or malignant melanoma, a squamous cell carcinoma or precursors thereof in an accurate and reliable way as claimed. This includes using measured impedances of the skin and reference data to determine whether the obtained impedance values indicate the diseased condition. In one non-limiting form of the invention, the impedance is measured at different depths (e.g. at five depths) and different frequencies (e.g. 31 logarithmically distributed frequencies from 1 kHz to 1 MHz).

In contrast to the present invention in which the present apparatus and technique determine a diseased condition using impedance values measured at specific locations of a patients skin, Davies discloses a method and apparatus for detecting abnormal tissue by measuring transport alterations in mucosal tissues. Davies measures a baseline level of transepithelial DC potential, impedance or other electrophysiological property that is sensitive to alteration in transport in epithelia. This baseline is measured in the tissue and evaluated. In order to enhance this transportation, an agent may be introduced to make it possible to detect the transport alteration and the transepithelial DC potential and/or impedance of the tissue are then measured. Based on the agent introduced and the

measured electrophysiological parameter, the condition of the tissue is determined (Davies col. 6, lines 23-48). Accordingly, Davies aims not primarily at measuring the impedance but any electrophysiological parameter that reflects or makes it possible to detect alterations in the transport, where impedance and transepithelial DC potential are examples of such parameters.

If the technique (method and device) according to Davies were to be modified to be used to measure the impedance in accordance with the claimed present invention, the skilled person would obtain diluted impedance data which, in turn, would result in an unspecific diagnose. This is due to the fact that, even if the penetration depth can be adjusted by spaced electrodes, so that the current may reach the skin layer beneath the stratum corneum, where the most valuable information about the skin condition can be obtained, the current must still pass through the stratum corneum. Thus, the important and necessary information about skin cancer will be overshadowed by irrelevant information from stratum corneum. It is known that α-dispersion from the stratum corneum is broad and large and may overshadow impedance data obtained from the skin underneath. Accordingly, modifying Davies to measure impedance as claimed would not produce the beneficial diagnostic technique which inherently follows from the claimed method and device. Therefore, one would have had no reason to modify Davies to measure impedance as claimed, as the resulting method would not be useful in diagnosis.

Based on the foregoing, it will be clear that the device of Davies and the techniques disclosed are directed to a completely different manner of diagnosing a diseased condition from the method and apparatus claimed. Further, it will be clear that

modifying the technique of Davies to measure impedance as claimed in no way makes the present invention obvious.

Moreover, one would not modify the disclosure of Davies to incorporate aspects of the device of Stemme in that Stemme is directed to a completely different method/technique from that of Davies. Therefore, one skilled in the art would have no incentive to replacing the electrode of Davies with the electrode of Stemme. Specifically, Stemme discloses an ultra specific technique and device for accurately measuring or sending biopotentials at the stratum germinativum layer of patient's skin. The method and device (spiked electrode) are highly specialized to accommodate issues associated with these measurements. The electrode includes a plurality of signal carrying spikes, each having a length being sufficient to penetrate the skin of a subject and to extend into the stratum germinativum. However, as mentioned, for example, in Stemme claim 1 and at page 9, Stemme is directed at sensing biopotentials. A biopotential is an electrical potential of biological origin. Examples include a resting potential across the membrane of a living cell the action potential of a neuron during depolarization and repolarization (e.g. cells of the brain give rise to EEG) and the sum of a number of myoelectrical signals (e.g. heart muscle gives rise to the ECG).

Stemme accommodates measuring these electrical potentials using its probe. One skilled in the art will know that EEG and ECG signals are small at the body surface, which is not a problem, itself, since amplification can be adjusted as needed, and a perfect differential amplifier would have practically infinite input impedance and infinite CMRR (common mode rejection ratio). The desired biopotential exist equally inside and

outside the stratum corneum (the very thin, dead, keratinized outermost layer of the skin). However, if the amplifier has suboptimal input impedance, a current will flow through the stratum corneum into the amplifier input, thereby causing a potential drop across the stratum corneum, and the measured biopotential will decrease with that amount. In addition, imbalance in the tissue/electrode interface impedance in a differential pair of contact electrodes will convert a common mode signal (typically electromagnetic interference from neighbouring installations, such as light tubes, computers and other devices) into a differential signal by different voltage division between each tissue/electrode impedance and the amplifier input impedances. Since part of the common mode interference signal then becomes a differential mode signal, high CMRR will not be able to eliminate such artefacts. Again, this is due to the limited input impedance of the amplifier, but would not cause any problem if the tissue/electrode interface impedance were identical at each differential pair, which is practically impossible to achieve.

The problem might become less with lower tissue/electrode impedance, which can be achieved by application of conductive gel between the actual electrode and the skin, by removing the dry stratum corneum mechanically (by grinding or cutting), or destroying it chemically (by application of a "penetration enhancer" such as sodium lauryl sulphate, which destroys the skin barrier function residing in the stratum corneum) – or one can short circuit the stratum corneum by inserting electrodes into the skin or even through the skin into underlying tissue such as muscle, i.e. more or less invasive electrodes. On the other hand, none of this is necessary for measuring biopotentials from

the body surface if the performance of the differential amplifier is sufficient, having both high enough input impedance and high enough CMRR.

However, Stemme's approach to improve the performance of the measurements of biopotentials is to optimize the frequency used for the measurements. As stated in Stemme paragraph [0049]:

> *"The ESEI [electrode-skin-electrode impedance [our note]] is dependent on the measurement frequency."*

In connection to this, a frequency spectrum of 0.5 to 500 Hz is discussed and it is stated that

> *"...this includes the interval of for biomedical applications."*

Further, in Stemme paragraph [0054] it is stated:

> *"The obtained electrical signals are stable with low noise levels even at low frequencies."*

Thus, Stemme teaches that the frequency should be optimized in order to improve the measurements.

In view of the foregoing, it would be clear that the one of ordinary skill in the art would not have combined the diagnostic technique and device of Davies with the electrode and technique to measure biopotentials of Stemme to arrive at the claimed invention. As illustrated in great detail above, the problems and solutions for skin electrodes in measuring biopotentials (Stemme) are of a completely different nature in comparison to the problems and solutions for skin electrodes in measuring impedance. (Davies) Accordingly, there is no incentive for one of ordinary skill in the art to combine

the dissimilar and incompatible disclosures of Davies and Stemme, since Stemme does in fact solve a completely different problem than the problem outlined in Davies.

Further, one skilled in the art would have seen no benefit for modifying Davies to incorporate the electrode of Stemme. Although, in the Office Action, page 5, it was alleged that the reason one would combine the spiked electrode of Stemme with Davies is based on a statement in Davies that a series of electrodes could be used (Davies, col. 13, lines 55-65), Davies in now way teaches or makes obvious the use of a spiked electrode as in Stemme. Most importantly, no where in Davies is there any disclosure which would lead one of ordinary skill in the art to measure impedance as claimed. Only through impermissive hindsight would one know to measure impedance was claimed and using the device as claimed. Most importantly, nowhere does Davies teach or in any way make obvious measuring impedance in the layer of the skin as claimed. Therefore, contrary to the assertion in the Office Action, Davies provides absolutely no disclosure which would lead one of ordinary skill in the art to use the spike electrode of Stemme.

Furthermore, if the skilled man, in spite of these facts, would combine Davies and Stemme, he or she would not obtain the present invention due to the fact that Stemme does not present a probe adapted for measuring bioimpedance. In fact, Stemme does not provide the skilled man with any indications how to modify the conventional probe to obtain a probe adapted to measure bioimpedance. Accordingly, the combination would result in an inoperable method or technique. In other words, one would not be able to practice the method and apparatus as claimed.

Further, if the skilled man, for the sake of argument, would combine Davies and Stemme, he would be lead in a different direction than the present invention and he would encounter problems requiring inventive skills to solve. For example, he would be led to modify the amplifier circuit in order to improve amplification or to optimize the frequency used for the measurement to reduce the noise. Further, the introduced agent, as suggested by Davies, which may include agonists or antagonists of specific ion transport and electrical activity, ionic substitutions and/or hormonal or growth factor stimulation or inhibition of electrical activity may influence the measurements and this influence has to be filtered off.

Based on the foregoing, one of ordinary skill in the art would not be led to the present invention by combining Davies and Stemme. Applicants respectfully submit that all pending claims are not obvious from Davies in view of Stemme, and request that the rejection to the claims as being obvious in view of Davies and Stemme be withdrawn.

In view of the foregoing, Applicants respectfully submit that the present application is in condition for allowance.

Respectfully submitted,

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